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(54) Title: NOVEL BICYCLIC AND TRICYCLIC CANNABINOIDS

(57) Abstract: Novel bicyclic-cannabinoids and hexahydrocannabinol analogs are presented. These compounds, when administered in a therapeutically effective amount to an individual or animal, results in a sufficiently high level of that compound in the individual or animal to cause a physiological response. The physiological response useful to treat a number of physiological conditions.

NOVEL BICYCLIC AND TRICYCLIC CANNABINOIDS

Field of the Invention

The present invention relates generally to cannabinoid analogs. The invention is more particularly concerned with new and improved bicyclic and tricyclic cannabinoids exhibiting high binding affinities for cannabinoid receptors, pharmaceutical preparations employing these analogs and methods of administering therapeutically effective amounts of the analogs to provide a physiological effect.

Background of the Invention

The classical cannabinoid Δ^9-Tetrahydrocannabinol (Δ^9-THC) is the major active constituent extracted from Cannabis sativa. The effects of cannabinoids are due to an interaction with specific high-affinity receptors. Presently, two cannabinoid receptors have been characterized: CB1, a central receptor found in the mammalian brain and a number of other sites in the peripheral tissues and CB2, a peripheral receptor found principally in cells related to the immune system. The CB1 receptor is believed to mediate the psychoactive properties, associated with classical cannabinoids. Characterization of these receptors has been made possible by the development of specific synthetic ligands such as the agonists WIN 55212-2 and CP 55,940.

In addition to acting at the cannabinoid receptors, cannabinoids such as Δ^9-THC also affect cellular membranes, thereby producing undesirable side effects such as drowsiness, impairment of monoamine oxidase function and impairment of non-receptor mediated brain function. The addictive and psychotropic properties of some cannabinoids also limit their therapeutic value.

The pharmacological effects of cannabinoids pertain to a variety of areas such as the central nervous system, the cardiovascular system, the immune system and/or endocrine system. More particularly, compounds possessing an affinity for either the CB1 or the CB2 cannabinoid receptors are useful as agents: acting on the central nervous system and immunomodulators; in thymic

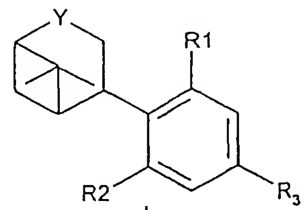
disorders; vomiting; myorelaxation; various types of neuropathy; memory disorders; dyskinesia; migraine; multiple sclerosis; asthma; epilepsy; glaucoma; in anticancer chemotherapy; in ischemia and angor; in orthostatic hypotension; and in cardiac insufficiency.

Currently known bicyclic-cannabinoids and hexahydrocannabinol analogs contain a linear alkyl side chain at the C - 3 position. This linear alkyl side chain at the C - 3 position is a key pharmacophore in classical cannabinoids and considered essential for cannabinoid receptor activity. Structure Activity Relationship (SAR) studies suggest that in known cannabinoids, a 1,1 - dimethylheptyl or a 1,2 - dimethylheptyl side chain is optimal for cannabinoid activity. Additionally, known hexahydrocannabinol derivatives usually possess a carbonyl group in the C - 9 position or a hydroxy group in the C - 9 or C - 11 positions. This ''northern'' functionality plays an important role on the cannabinoid structure, associated with cannabimimetic activity. The presence of a C - 9 carbonyl group or a C – 9 or C - 11 hydroxy group is also known to significantly enhance the potency of cannabinoids.

Summary of the Invention

Briefly stated, one aspect of the present invention comprises novel bicyclic-cannabinoids and hexahydrocannabinol analogs, and their physiologically acceptable salts. In some variations the inventive hexahydrocannabinol analogs include hitherto unknown side chain moieties at the C - 3 position. In some variations the inventive hybrid type bicyclic-cannabinoids have terpene functionality combined with novel resorcinol moieties. The invention includes both the (-) and (+) enantiomers and all isomers. Some embodiments of this aspect are represented by the following compound formulas I, II, III, IV, V, VI.

Compound formula I



I

wherein Y comprises =C=O, =CH–$(CH_2)_f$–Y_1–$(CH_2)_g$–Y_2, =C=N–Y_3, =CH–NY_4Y_5, =CH–$(CH_2)_h$–Y_6, –C(O)N(Y_7)– , –N(Y_7)C(O)–, =NY_{11}, =N–$(CH_2)_f$–Y_1–$(CH_2)_g$–Y_2, a spirocycle, or CY_9Y_{10}, including all isomers.

Y_1 independently comprises O, CO, C(O)O, OCO or CH_2.

Y_2 independently comprises H, halogen, CN, CF_3, N_3, OH, COOH, alkoxy, acyloxy, NCS, NCO or NY_7Y_8.

Y_3 independently comprises –OH, –NH_2, alkoxy, alkyl, –$(CH_2)_n$–$NR_{10}R_{11}$, –$(CH_2)_n$–CO_2R where R comprises H or alkyl, –O–$(CH_2)_n$–$NR_{10}R_{11}$, –O–$(CH_2)_n$–CO_2R or –O–$(CH_2)_n$–$CONR_{10}R_{11}$.

Y_4 independently comprises H, OH, alkoxy or alkyl.

Y_5 independently comprises H, OH, alkoxy or alkyl, wherein Y_4 and Y_5 cannot both be OH and wherein Y_4 and Y_5 cannot both be alkoxy.

Y_6 independently comprises H, halogen, CN, COOH, COalkyl, CF_3, SO_2alkyl, COfluoroalkyl, N_3, OH, alkoxy, acyloxy, NCS, NCO or NY_7Y_8.

Y_7 independently comprises H, alkyl, hydroxyalkyl, an aromatic ring, an aromatic ring substituted by at least one member selected from alkyl, alkoxy, halogen and CF_3, a heterocyclic ring or a heteroaromatic ring.

Y_8 independently comprises H, alkyl, hydroxyalkyl, an aromatic ring, an aromatic ring substituted by at least one member selected from alkyl, alkoxy, halogen and CF_3, a heterocyclic ring or a heteroaromatic ring.

Alternatively, Y_7 and Y_8 taken together comprise part of a 3 to 7 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S.

Y_9 independently comprises H, alkyl or alkoxycarbonylmethyl.

Y_{10} independently comprises H, alkyl or alkoxycarbonylmethyl.

Y_{11} independently comprises H, alkyl, CO, CN, CO–alkyl, SO_2–akyl or CF_3. f comprises an integer from 0 to about 5.

g comprises an integer from 0 to about 5.

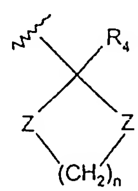
h comprises an integer from 0 to about 5.

n comprises an integer from 0 to about 4.

R_1 and R_2 each independently comprise H, OH, halogen, alkyl, –O–alkyl, NH_2, NO_2, CN, acyl, aroyl, benzoyl, substituted benzoyl, arylalkyl, substituted arylalkyl, phenacyl, substituted phenacyl, –O–alkyl–$NR_{10}R_{11}$, –O–alkyl–COOR where R comprises H or alkyl, –O–alkyl–$CONR_{10}R_{11}$, $OCOCH_3$, –N(alkyl)$_2$, –CO(alkyl)X or –OCO(alkyl)X where X comprises H, dialkylamino, a cyclic amine, a carbocyclic ring, a heterocyclic ring, an aromatic ring or a heteroaromatic.

R_{10} and R_{11} each independently comprise H, alkyl, hydroxyalkyl or R_{10} and R_{11} together comprise part of a 3 to 7 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S.

R_3 comprises



wherein each Z independently comprises $CR_{12}R_{13}$ where R_{12} and R_{13} each independently comprise H, alkyl, S, O, NH, $N(CH_3)$, SO or SO_2.

R_4 comprises $-(CH_2)_j-R_5$, $-(CH_2)_j-A-(CH_2)_k-R_5$ or $-(CH_2)_j-A-(CH_2)_k-B-R_5$.

A and B each independently comprise $-CH_2-CH_2-$, $-CH{=}CH-$, $-C{\equiv}C-$, O, S, SO, SO_2 or NH.

R_5 comprises H, halogen, CN, CF_3, N_3, COOH, NH_2, $N(CH_3)_2$, $\oplus N(CH_3)_3$, Sn(alkyl)$_3$, phenyl, COOR where R comprises H or alkyl, a carbocylic ring, a heterocyclic ring, an aromatic ring,

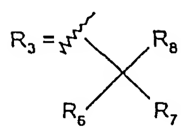
a heteroaromatic ring, a polycarbocyclic ring structure having 2 to about 5 rings, a polyheterocyclic ring structure having 2 to about 5 rings or $CONR_{10}R_{11}$ where R_{10} and R_{11} each independently comprise H, alkyl, hydroxyalkyl or R_{10} and R_{11} together comprise part of a 5 or 6 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S.

n comprises an integer from 0 to about 4.

j comprises an integer from 0 to about 7.

k comprises an integer from 0 to about 7.

In one variation of the invention R_3 comprises



wherein R_6 and R_7 each independently comprise H or alkyl.

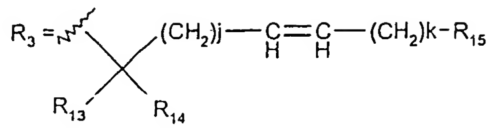
R_8 comprises $-(CH_2)_j-C{\equiv}C-(CH_2)_k-R_9$.

R_9 comprises H, halogen, CN, CF_3, N_3, COOH, NH_2, $N(CH_3)_2$, $\oplus N(CH_3)_3$, $Sn(alkyl)_3$, phenyl, COOR where R comprises H or alkyl, a carbocylic ring, a heterocyclic ring, an aromatic ring, a heteroaromatic ring, a polycarbocyclic ring structure having 2 to about 5 rings, a polyheterocyclic ring structure having 2 to about 5 rings or $CONR_{10}R_{11}$ where R_{10} and R_{11} each independently comprise H, alkyl, hydroxyalkyl or R_{10} and R_{11} together comprise part of a 5 or 6 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S.

j comprises an integer from 0 to about 7.

k comprises an integer from 0 to about 7.

In another variation of the invention (compound formula II) R_1 and R_2 each independently comprise H, OH, alkyl or alkoxy and R_3 comprises:



wherein R_{13} and R_{14} each independently comprise H or alkyl.

R_{15} comprises H, halogen, CN, CF_3, N_3, COOH, NH_2, $N(CH_3)_2$, $\oplus N(CH_3)_3$, $Sn(alkyl)_3$, phenyl, COOR where R comprises H or alkyl, a carbocylic ring, a heterocyclic ring, an aromatic ring, a heteroaromatic ring, a polycarbocyclic ring structure having 2 to about 5 rings, a polyheterocyclic ring structure having 2 to about 5 rings or $CONR_{10}R_{11}$ where R_{10} and R_{11} each independently comprise H, alkyl, hydroxyalkyl or R_{10} and R_{11} together comprise part of a 5 or 6 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S.

j comprises an integer from 0 to about 7.

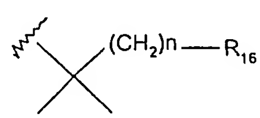
k comprises an integer from 0 to about 7.

In another variation of the invention (compound formula III) Y comprises $=CH-(CH_2)_h-Y_6$..

Y_6 comprises I, CN or N_3 and h comprises an integer from about 1 to about 3, or Y_6 comprises I or N_3 and h comprises an integer from 0 to about 3.

R_1 and R_2 each independently comprise H, OH, alkyl or alkoxy.

R_3 comprises:

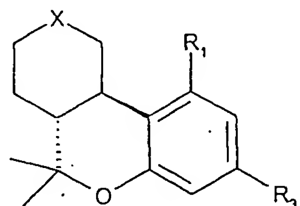


wherein R_{16} comprises H, halogen, CN, CF_3, N_3, COOH, NH_2, $N(CH_3)_2$, $\oplus N(CH_3)_3$, $Sn(alkyl)_3$, phenyl, COOR where R comprises H or alkyl, a carbocylic ring, a heterocyclic ring, an aromatic ring, a heteroaromatic ring, a polycarbocyclic ring structure having 2 to about 5 rings, a polyheterocyclic ring structure having 2 to about 5 rings or $CONR_{10}R_{11}$ where R_{10} and R_{11} each independently comprise H, alkyl,

hydroxyalkyl or R_{10} and R_{11} together comprise part of a 5 or 6 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S.

n comprises an integer from 0 to about 7.

Another variation of the invention (compound formula IV) has the following structure:



IV

wherein X comprises =C=O, =CH–$(CH_2)_f$–X_1–$(CH_2)_g$–X_2, =C=N–X_3, =CH–NX_4X_5, =CH–$(CH_2)_h$–X_6, –C(O)N(X_7)– , –N(X_7)C(O)–, =NX_{11}, =N–$(CH_2)_f$–X_1–$(CH_2)_g$–X_2, a spirocycle, or CX_9X_{10}, including all isomers.

X_1 independently comprises O, CO, C(O)O, OCO or CH_2.

X_2 independently comprises H, halogen, CN, CF_3, N_3, OH, COOH, alkoxy, acyloxy, NCS, NCO or NX_7X_8.

X_3 independently comprises –OH, –NH_2, alkoxy, alkyl, –$(CH_2)_n$–$NR_{10}R_{11}$, –$(CH_2)_n$–CO_2R where R comprises H or alkyl, –O–$(CH_2)_n$–$NR_{10}R_{11}$, –O–$(CH_2)_n$–CO_2R or –O–$(CH_2)_n$–$CONR_{10}R_{11}$.

X_4 independently comprises H, OH, alkoxy or alkyl.

X_5 independently comprises H, OH, alkoxy or alkyl, wherein X_4 and X_5 cannot both be OH and wherein X_4 and X_5 cannot both be alkoxy.

X_6 independently comprises H, halogen, CN, COOH, COalkyl, CF_3, SO_2alkyl, COfluoroalkyl, N_3, OH, alkoxy, acyloxy, NCS, NCO or NX_7X_8.

X_7 independently comprises H, alkyl, hydroxyalkyl, an aromatic ring, ar aromatic ring substituted by at least one member selected from alkyl, alkoxy, halogen and CF_3, a heterocyclic ring or a heteroaromatic ring.

X_8 independently comprises H, alkyl, hydroxyalkyl, an aromatic ring, an

aromatic ring substituted by at least one member selected from alkyl, alkoxy, halogen and CF_3, a heterocyclic ring or a heteroaromatic ring. Alternatively, X_7 and X_8 taken together comprise part of a 3 to 7 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S.

X_9 independently comprises H, alkyl or alkoxycarbonylmethyl.

X_{10} independently comprises H, alkyl or alkoxycarbonylmethyl.

X_{11} independently comprises H, alkyl, CO, CN, COalkyl, SO_2alkyl or CF_3.

f comprises an integer from 0 to about 3.

g comprises an integer from 0 to about 3.

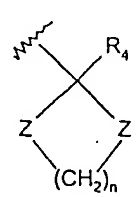
h comprises an integer from 0 to about 3.

n comprises an integer from 0 to about 4.

R_1 independently comprises H, OH, halogen, alkyl, –O–alkyl, NH_2, NO_2, CN, acyl, aroyl, benzoyl, substituted benzoyl, arylalkyl, substituted arylalkyl, phenacyl, substituted phenacyl, –O–alkyl–$NR_{10}R_{11}$, –O–alkyl–COOR where R comprises H or alkyl, –O–alkyl–$CONR_{10}R_{11}$, $OCOCH_3$, –N(alkyl)$_2$, –CO(alkyl)X or –OCO(alkyl)X where X comprises H, dialkylamino, a cyclic amine, a carbocyclic ring, a heterocyclic ring, an aromatic ring or a heteroaromatic.

R_{10} and R_{11} each independently comprise H, alkyl, hydroxyalkyl or R_{10} and R_{11} together comprise part of a 3 to 7 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S.

R_3 comprises



wherein each Z independently comprises $CR_{12}R_{13}$ where R_{12} and R_{13} each independently comprise H, alkyl, S, O, NH, $N(CH_3)$, SO or SO_2.

R_4 comprises $-(CH_2)_j-R_5$, $-(CH_2)_j-A-(CH_2)_k-R_5$ or $-(CH_2)_j-A-(CH_2)_k-B-R_5$.

A and B each independently comprise $-CH_2-CH_2-$, $-CH=CH-$, $-C\equiv C-$, O, S, SO, SO_2 or NH.

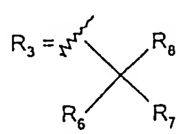
R_5 comprises H, halogen, CN, CF_3, N_3, COOH, NH_2, $N(CH_3)_2$, $\oplus N(CH_3)_3$, Sn(alkyl)$_3$, phenyl, COOR where R comprises H or alkyl, a carbocylic ring, a heterocyclic ring, an aromatic ring, a heteroaromatic ring, a polycarbocyclic ring structure having 2 to about 5 rings, a polyheterocyclic ring structure having 2 to about 5 rings or $CONR_{10}R_{11}$ where R_{10} and R_{11} each independently comprise H, alkyl, hydroxyalkyl or R_{10} and R_{11} together comprise part of a 5 or 6 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S.

n comprises an integer from 0 to about 4.

j comprises an integer from 0 to about 7.

k comprises an integer from 0 to about 7.

In one variation of the invention, R_3 comprises:



wherein R_6 and R_7 each independently comprise H or alkyl.

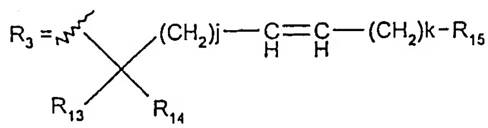
R_8 comprises $-(CH_2)_j-C\equiv C-(CH_2)_k-R_9$.

R_9 comprises H, halogen, CN, CF_3, N_3, COOH, NH_2, $N(CH_3)_2$, $\oplus N(CH_3)_3$, Sn(alkyl)$_3$, phenyl, COOR where R comprises H or alkyl, a carbocylic ring, a heterocyclic ring, an aromatic ring, a heteroaromatic ring, a polycarbocyclic ring structure having 2 to about 5 rings, a polyheterocyclic ring structure having 2 to about 5 rings or $CONR_{10}R_{11}$ where R_{10} and R_{11} each independently comprise H, alkyl, hydroxyalkyl or R_{10} and R_{11} together comprise part of a 5 or 6 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S.

j comprises an integer from 0 to about 7.

k comprises an integer from 0 to about 7.

In another variation of the invention (compound formula V) R_1 comprises H, OH, alkyl or alkoxy and R_3 comprises:



wherein R_{13} and R_{14} each independently comprise H or alkyl.

R_{15} comprises halogen, CN, CF_3, N_3, COOH, NH_2, $N(CH_3)_2$, $\oplus N(CH_3)_3$, $Sn(alkyl)_3$, phenyl, COOR where R comprises H or alkyl, a carbocylic ring, a heterocyclic ring, an aromatic ring, a heteroaromatic ring, a polycarbocyclic ring structure having 2 to about 5 rings, a polyheterocyclic ring structure having 2 to about 5 rings or $CONR_{10}R_{11}$ where R_{10} and R_{11} each independently comprise H, alkyl, hydroxyalkyl or R_{10} and R_{11} together comprise part of a 5 or 6 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S.

j comprises an integer from 0 to about 7.

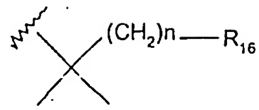
k comprises an integer from 0 to about 7.

In another variation of the invention (compound formula VI) X comprises $=CH-(CH_2)_h-X_6$.

X_6 independently comprises I, CN, N_3 or COOH and h comprises an integer from about 1 to about 3, or X_6 comprises I, N_3 or COOH and h comprises an integer from 0 to about 3, including all isomers.

R_1 independently comprises H, OH, alkyl or alkoxy.

R_3 comprises:



R_{16} comprises H, halogen, CN, CF_3, N_3, COOH, NH_2, $N(CH_3)_2$, $\oplus N(CH_3)_3$, Sn(alkyl)$_3$, phenyl, COOR where R comprises H or alkyl, a carbocylic ring, a heterocyclic ring, an aromatic ring, a heteroaromatic ring, a polycarbocyclic ring structure having 2 to about 5 rings, a polyheterocyclic ring structure having 2 to about 5 rings or $CONR_{10}R_{11}$ where R_{10} and R_{11} each independently comprise H, alkyl, hydroxyalkyl or R_{10} and R_{11} together comprise part of a 5 or 6 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S.

n comprises an integer from 0 to about 7.

Unless otherwise specifically defined, "acyl" refers to the general formula –C(O)alkyl.

Unless otherwise specifically defined, "acyloxy" refers to the general formula –O–acyl.

Unless otherwise specifically defined, "alcohol" refers to the general formula alkyl–OH.

Unless otherwise specifically defined, "alkyl" refers to a linear, branched or cyclic alkyl group having from 1 to about 9 carbon atoms including, for example, methyl, ethyl, propyl, butyl, hexyl, octyl, isopropyl, isobutyl, tert-butyl, cyclopropyl, cyclohexyl, cyclooctyl, vinyl and allyl. Unless otherwise specifically defined, an alkyl group can be saturated or unsaturated and substituted or unsubstituted. Unless otherwise specifically limited, a cyclic alkyl group includes monocyclic, bicyclic and polycyclic rings, for example norbornyl, adamantyl and related terpenes.

Unless otherwise specifically defined, "alkoxy" refers to the general formula –O–alkyl.

Unless otherwise specifically defined, "alkylmercapto" refers to the general formula –S–alkyl.

Unless otherwise specifically defined, "alkylamino" refers to the general formula –(NH)–alkyl.

Unless otherwise specifically defined, "di-alkylamino" refers to the general formula –N–(alkyl)$_2$. Unless otherwise specifically limited di-alkylamino includes cyclic amine compounds such as piperidine and morpholine.

Unless otherwise specifically defined, an aromatic ring is an unsaturated ring structure having about 5 to about 6 ring members and including only carbon as ring atoms. Unless otherwise specifically defined, an aromatic ring can be substituted or unsubstituted.

Unless otherwise specifically defined, "aryl" refers to an aromatic ring system substituted or unsubstituted, that includes only carbon as ring atoms, for example phenyl, biphenyl or napthyl.

Unless otherwise specifically defined, "aroyl" refers to the general formula –C(=O)–aryl.

Unless otherwise specifically defined, a carbocyclic ring is a ring structure having about 3 to about 8 ring members, substituted or unsubstituted, that includes only carbon as ring atoms, for example, benzene or cyclohexane.

Unless otherwise specifically defined, "halogen" refers to an atom selected from fluorine, chlorine, bromine and iodine.

Unless otherwise specifically defined, a heteroaromatic ring is an unsaturated ring structure having about 5 to about 8 ring members, substituted or unsubstituted, that has carbon atoms and one or more heteroatoms, including oxygen, nitrogen and/or sulfur, as ring atoms, for example, pyridine, furan, quinoline, and their derivatives.

Unless otherwise specifically defined, a heterocyclic ring is a saturated ring structure having about 3 to about 8 ring members, substituted or unsubstituted, that has carbon atoms and one or more heteroatoms, including oxygen, nitrogen and/or sulfur, as ring atoms, for example, piperidine, morpholine, piperazine, and their derivatives. Unless otherwise specifically limited a heterocyclic ring

includes monocyclic, bicyclic and polycyclic rings, for example azaadamantyl and tropanyl.

Unless otherwise specifically defined, the term "phenacyl" refers to the general formula –phenyl–acyl.

Unless otherwise specifically defined, a spirocycle refers to a ring system wherein a single atom is the only common member of two rings. A spirocycle can comprise a saturated carbocyclic ring comprising about 3 to about 8 ring members, a heterocyclic ring comprising about 3 to about 8 ring atoms wherein up to about 3 ring atoms may be N, S, or O or a combination thereof.

Substituent groups for the above moieties useful in the invention are those groups that do not significantly diminish the biological activity of the inventive compound. Substituent groups that do not significantly diminish the biological activity of the inventive compound include, for example, –OH, $-NH_2$, halogen, –CN, $-NO_2$, –NHalkyl, $-N(alkyl)_2$, $-CF_3$, –NCS, azido, –CONHalkyl, –NHCOalkyl, sulfonamide, alkyl, alkoxy, thioalkoxy and alcohol.

Testing of the inventive compounds for their affinities for the central (CB1) and peripheral (CB2) cannabinoid receptors, showed a high affinity for the two cannabinoid receptors. Thus, another aspect of the invention is use of at least one of the inventive compounds, and physiologically acceptable salts thereof, to stimulate cannabinoid receptors.

Some of the inventive analogs showed high selectivity for the CB2 receptor. These inventive CB2 selective analogs are able to stimulate the CB2 receptor without affecting the central (CB1) receptor to the same degree. Therefore, another aspect of the invention is use of at least one of the inventive compounds, and physiologically acceptable salts thereof, to preferentially stimulate the CB2 receptor.

The inventive bicyclic-cannabinoids and hexahydrocannabinol analogs described herein, and physiologically acceptable salts thereof, have pharmacological properties when administered in therapeutically effective amounts for providing a physiological effect useful to treat central and peripheral pain, neuropathy, neurodegenerative diseases including multiple sclerosis,

Parkinson's disease, Huntington's chorea, Alzheimer's disease; mental disorders such as schizophrenia and depression; to prevent or reduce endotoxic shock and hypotensive shock; to modulate appetite; to modulate the immune system; to reduce fertility; to prevent or reduce diseases associated with motor function such as Tourette's syndrome; to prevent or reduce inflammation; to provide neuroprotection and to suppress memory and produce peripheral vasodilation; to treat epilepsy, glaucoma, nausea associated with cancer chemotherapy and AIDS wasting syndrome as well as other ailments in which cannabinoid system is implicated. Thus, another aspect of the invention is the administration of a therapeutically effective amount of an inventive compound, or a physiologically acceptable salt thereof, to an individual or animal to provide a physiological effect.

Description of Some Preferred Embodiments

As used herein a "therapeutically effective amount" of a compound, is the quantity of a compound which, when administered to an individual or animal, results in a discernible physiological effect in the individual or animal. The inventive compounds described herein, and physiologically acceptable salts thereof, have pharmacological properties when administered in therapeutically effective amounts for providing a physiological effect useful to treat a number of physiological conditions.

Typically, a "therapeutically effective amount" of an inventive compound is believed to range from about 5 mg/day to about 1,000 mg/day.

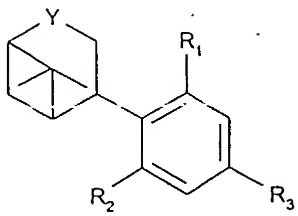
As used herein, an "individual" refers to a human. An "animal" refers to, for example, veterinary animals, such as dogs, cats, horses and the like, and farm animals, such as cows, pigs and the like.

The compound of the present invention can be administered by a variety of known methods, including, for example, orally, rectally, or by parenteral routes (e.g., intramuscular, intravenous, subcutaneous, nasal or topical). The form in which the compounds are administered will be determined by the route of administration. Such forms include, but are not limited to, capsular and tablet

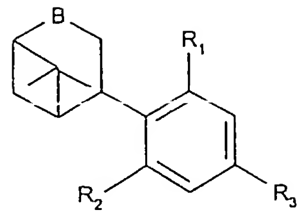
formulations (for oral and rectal administration), liquid formulations (for oral, intravenous, intramuscular, subcutaneous, ocular, intranasal, inhalation-based and transdermal administration) and slow releasing microcarriers (for rectal, intramuscular or intravenous administration). The formulations can also contain a physiologically acceptable vehicle and optional adjuvants, flavorings, colorants and preservatives. Suitable physiologically acceptable vehicles include, for example, saline, sterile water, Ringer's solution and isotonic sodium chloride solutions. The specific dosage level of active ingredient will depend upon a number of factors, including, for example, biological activity of the particular preparation, age, body weight, sex and general health of the individual being treated..

In one aspect of the invention the inventive compounds are generally represented by compound formulas I, II, III, IV, V, VI and include physiologically acceptable salts thereof.

Compound formulas I - VI



I



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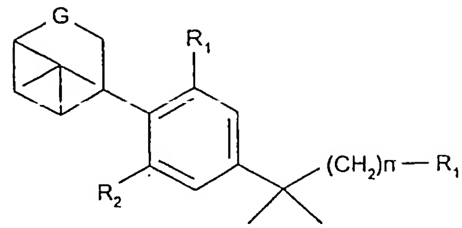

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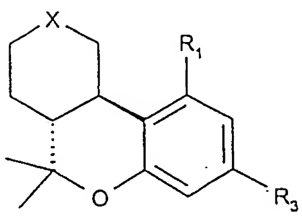
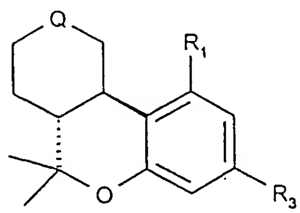
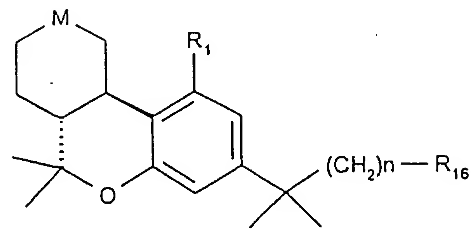


IV



V



VI

Some inventive analogs were tested for CB2 receptor binding affinity and for CB1 receptor affinity (to determine selectivity). As used herein, "binding affinity" is represented by the IC_{50} value which is the concentration of an analog required to occupy the 50% of the total number (Bmax) of the receptors. The lower the IC_{50} value the higher the binding affinity. As used herein an analog is said to have "binding selectivity" if it has higher binding affinity for one receptor compared to the other receptor; e.g. a cannabinoid analog which has an IC_{50} of 0.1 nM for CB1 and 10 nM for CB2, is 100 times more selective for the CB1 receptor. For the CB1 receptor binding studies, membranes were prepared from rat forebrain membranes according to the procedure of P.R. Dodd et al, <u>A Rapid Method for Preparing Synaptosomes: Comparison with Alternative Procedures</u>, Brain Res., 107 - 118 (1981). The binding of the novel analogues to the CB1 cannabinoid receptor was assessed as described in W.A. Devane et al, <u>Determination and Characterization of a Cannabinoid Receptor in a Rat Brain</u>, Mol. Pharmacol., 34, 605 - 613 (1988) and A. Charalambous et al, <u>5'-azido Δ^8 -THC: A Novel Photoaffinity Label for the Cannabinoid Receptor</u>, J. Med. Chem., 35, 3076 - 3079 (1992) with the following changes. The above articles are incorporated by reference herein.

Membranes, previously frozen at -80°C, were thawed on ice. To the stirred suspension was added three volumes of TME (25 mM Tris-HCl buffer, 5

mM $MgCl_2$ and 1 mM EDTA) at a pH 7.4. The suspension was incubated at 4°C for 30 min. At the end of the incubation, the membranes were pelleted and washed three times with TME.

The treated membranes were subsequently used in the binding assay described below. Approximately 30 μg of membranes were incubated in silanized 96-well microtiter plate with TME containing 0.1% essentially fatty acid-free bovine serum albumin (BSA), 0.8 nM [^{3}H] CP-55,940, and various concentrations of test materials in a final volume of 200 μL. The assays were incubated for 1 hour at 30 °C and then immediately filtered using Packard Filtermate 196 harvester and Whatman GF/C filterplates and washed with wash buffer (TME) containing 0.5% BSA. Radioactivity was detected using MicroScint 20 scintillation cocktail added directly to the dried filterplates, and the filterplates were counted using a Packard Instruments Top-Count. Nonspecific binding was assessed using 100 nM CP-55,940. Data collected from three independent experiments performed with duplicate determinations was normalized between 100% and 0% specific binding for [^{3}H] CP-55,940, determined using buffer and 100 nM CP-55,940. The normalized data was analyzed using a 4-parameter nonlinear logistic equation to yield IC_{50} values. Data from at least two independent experiments performed in duplicate was used to calculate IC_{50} values which were converted to K_i values using the assumptions of Cheng et al, Relationship Between the Inhibition Constant (K_i) and the concentration of Inhibitor which causes 50% Inhibition (IC_{50}) of an Enzymatic Reaction, Biochem. Pharmacol., 22, 3099-3102, (1973), which is incorporated by reference herein.

For the CB2 receptor binding studies, membranes were prepared from frozen mouse spleen essentially according to the procedure of P.R. Dodd et al, A Rapid Method for Preparing Synaptosomes: Comparison with Alternative Procedures, Brain Res., 226, 107 - 118 (1981) which is incorporated by reference herein. Silanized centrifuge tubes were used throughout to minimize receptor loss due to adsorption. The CB2 binding assay was conducted in the same manner as for the CB1 binding assay. The binding affinities (K_i) were also expressed in nanomoles (nM). Some of the synthesized analogs disclosed below

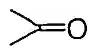
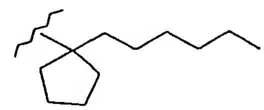
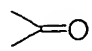
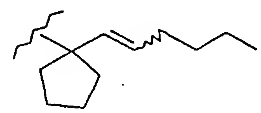
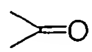
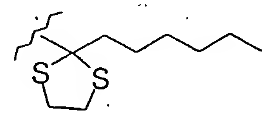
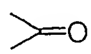
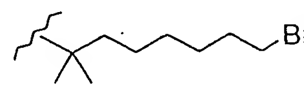
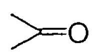
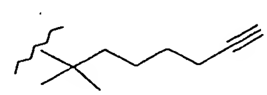
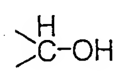
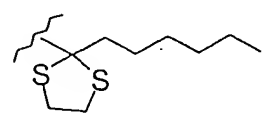
exhibited a selectivity for the CB2 receptor of from less than 10 fold to about 500 fold. Some of the synthesized analogs disclosed below exhibited a lesser selectivity for the CB1 receptor.

The following examples are given for purposes of illustration only in order that the present invention may be more fully understood. These examples are not intended to limit in any way the scope of the invention unless otherwise specifically indicated.

Examples:

Bicyclic-cannabinoid hybrids of compound formula I, II and III were synthesized with different R groups and different Y, B, G functionalities are depicted in Table 1. The CB1 and CB2 binding affinity value (Ki) for the synthesized analogs range between 31 – 224 nM and 0.2 – 77 nM respectively.

Table 1: Novel Bicyclic-cannabinoid analogs of compound formula I, II and III.

Compound number	Y, B, G Functionality	R_1	R_2	R_3
2a		OH	OH	
2b		OH	OH	
2c		OH	OH	
2d		OH	OH	
2e		OH	OH	
3		OH	OH	

Hexahydrocannabinol derivatives of compound formula IV, V and VI were synthesized with different R groups and different X, Q, M functionalities are depicted in Table 2. The CB1 and CB2 binding affinity value (Ki) for the synthesized analogs range between 0.1 – 12 nM and 0.2 – 14 nM respectively.

Table 2: Novel Hexahydrocannabinol analogs of compound formula IV, V and VI.

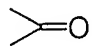
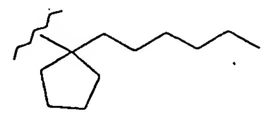
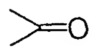
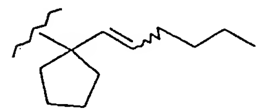
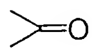
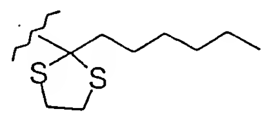
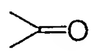
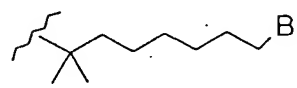
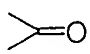
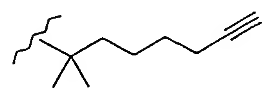
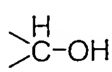
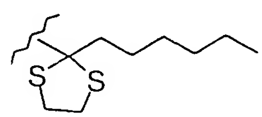
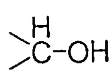
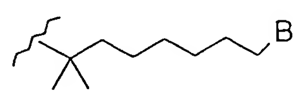
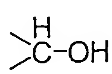
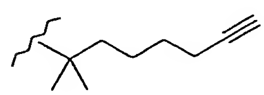
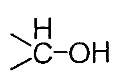
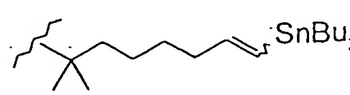
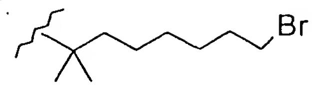
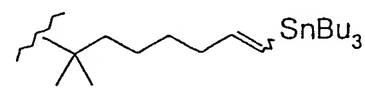
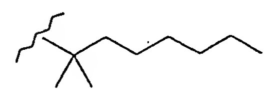
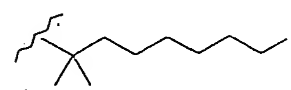
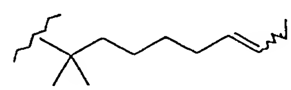
Compound number	X, Q, M Functionality	R_1	R_3
4a		OH	
4b		OH	
4c		OH	
4d		OH	
4e		OH	
5		OH	
6d		OH	
6e		OH	
6f		OH	

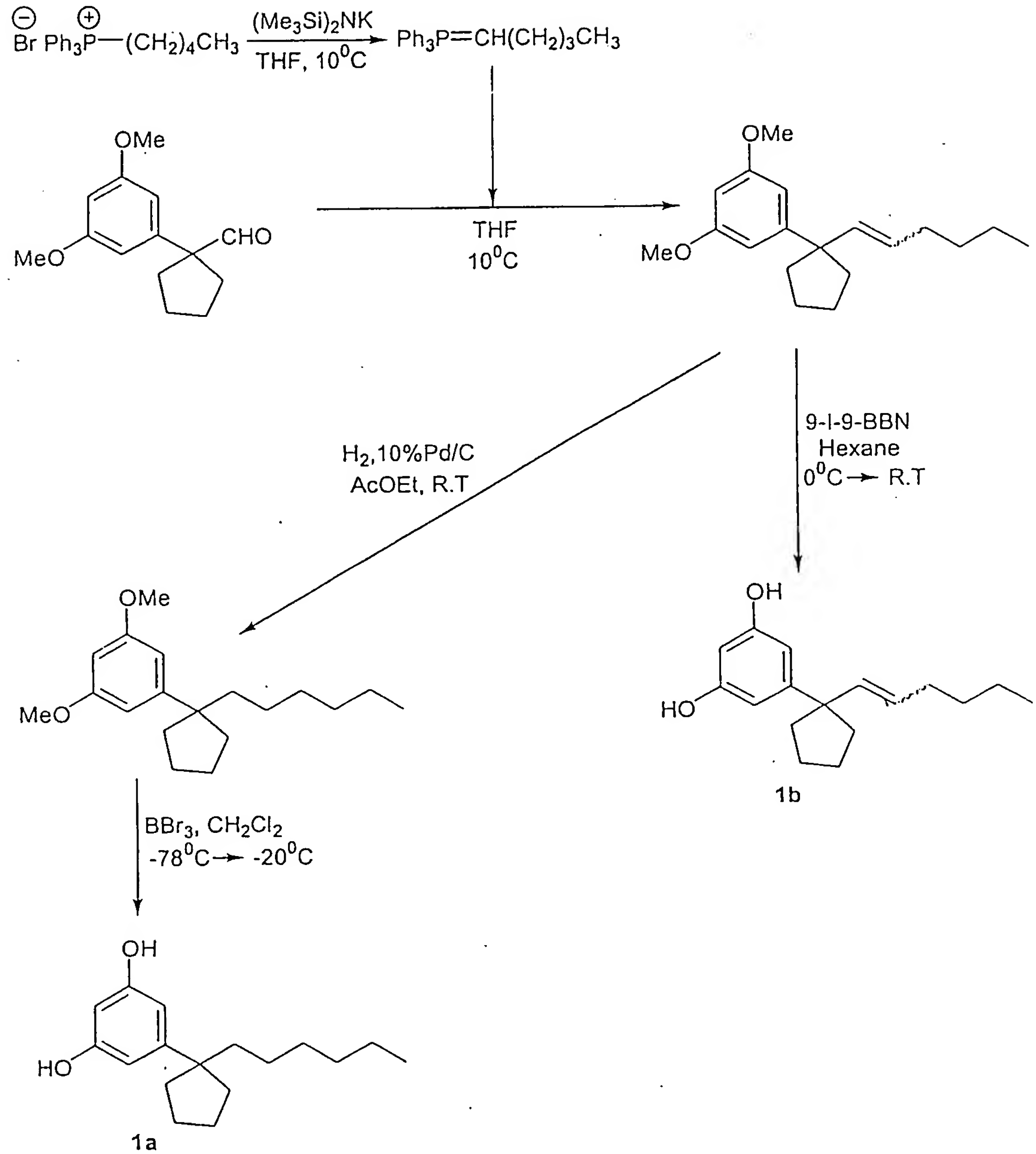
Table 2: continued

Compound number	X, Q, M Functionality	R_1	R_3
7d	$>$CH-N_3	OH	
7f	$>$CH-N_3	OH	
7g	$>$CH-N_3	OH	
8	$>$CH-N_3	OH	
9	$>$CH-N_3	OH	

<u>Preparation of compounds of compound formula I, II, III.</u>

1. Resorcinol synthesis

Resorcinol compounds 1a and 1b (shown in Scheme 1) were synthesized by a method depicted in Scheme 1, starting from (3,5-dimethoxyphenyl)cyclopentane carboxaldehyde, which was prepared by the method disclosed in Papahatjis et al. *Chemistry Letters*, 192 (2001), the content of which is hereby incorporated by reference.



Scheme 1

general procedure:

(Butylmethylene) triphenylphosphorane.

To a suspension of pentyltriphenylphosphonium bromide (5 equiv.) in dry THF (0.18M) at 0°C, under an argon atmosphere was added potassium bis(trimethylsilyl) amide (4.9 equiv.). The mixture was warmed to 10°C and

stirred for an additional 30 min to ensure complete formation of the orange ylide. The resulting slurry was used in the preparation of 1-(3,5-dimethoxyphenyl)-1-(hex-1-enyl)-cyclopentane.

1-(3,5-Dimethoxyphenyl)-1-(hex-1-enyl)-cyclopentane.

To the above slurry of (butylmethylene) triphenylphosphorane at 10°C under an argon atmosphere was added dropwise a solution of (3,5-dimethoxyphenyl)cyclopentane carboxaldehyde (1 equiv.) in dry THF (0.21M). The reaction was stirred for 45 min and upon completion was quenched by the addition of saturated aqueous ammonium chloride. The organic layer was separated and the aqueous phase was extracted twice with diethyl ether. The combined organic layer was washed with brine, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to give an oil. The crude product was purified through a short column of silica gel using 5% diethyl ether-petroleum ether as eluent to afford the title compound in 96% yield.

1-(3,5-Dimethoxyphenyl)-1-hexyl-cyclopentane.

To a solution of 1-(3,5-dimethoxyphenyl)-1-(hex-1-enyl)-cyclopentane (1 equiv.) in ethyl acetate (0.11M) was added 10% Pd/C (17%, w/w) and the resulting suspension was stirred vigorously under an hydrogen atmosphere, overnight at room temperature. The catalyst was removed by filtration through celite and the filtrate was evaporated under reduced pressure to afford the crude product. Purification through a short column of silica gel using 5% diethyl ether-petroleum ether yielded the title compound in 95% yield.

5-(1-Hexyl-cyclopentyl)resorcinol, (compound 1a).

To a solution of 1-(3,5-dimethoxyphenyl)-1-hexyl-cyclopentane (1 equiv.) in dry methylene chloride (0.04M) at -78°C under an argon atmosphere was added boron tribromide (2.5 equiv., 1M solution in methylene chloride). Following the addition, the reaction temperature was gradually raised over a period of 3 h to -20°C. Stirring was continued at that temperature until

completion of the reaction. Unreacted boron tribromide was destroyed by addition of methanol and ice at $0^{0}C$. The resulting mixture was warmed at room temperature, stirred for 40 min and the solvent was removed in vacuo. The residual oil was diluted with ethyl acetate and the solution was washed with saturated sodium bicarbonate, water and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography (40% diethyl ether-petroleum ether as eluent) afforded the title compound in 90% yield.

^1H NMR (500 MHz, $CDCl_3$) δ: 6.36 (d, J = 1.6Hz, 2H), 6.19 (t, J = 1.6Hz, 1H), 5.78 (brs, 2H, OH), 1.83 – 1.77 (m, 2H), 1.73 – 1.58 (m, 6H), 1.51 – 1.48 (m, 2H), 1.22 – 1.12 (m, 6H), 1.02 – 0.94 (m, 2H), 0.83 (t, J = 7.1Hz, 3H).

5-[1-(Hex-1-enyl)-cyclopentyl]resorcinol, (compound 1b)

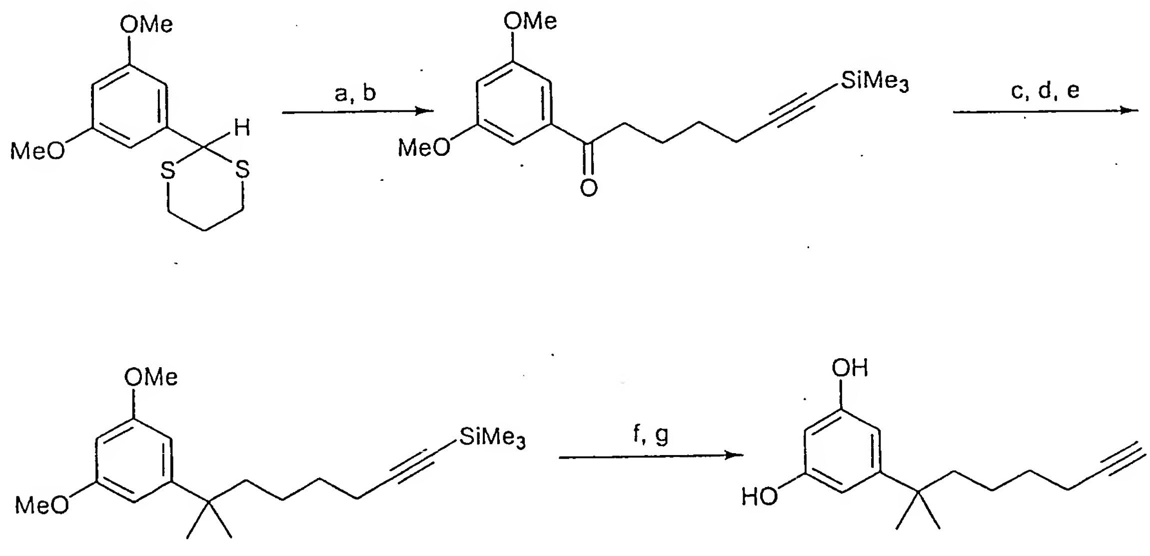
To a solution of 1-(3,5-dimethoxyphenyl)-1-(hex-1-enyl)-cyclopentane (1 equiv.) in dry hexane (0.05M) at 0°C under an argon atmosphere was added 9-iodo-9-BBN (2.3 equiv., 1M solution in hexane). The mixture was stirred at the same temperature for 3.5h and then the reaction temperature was raised to 27°C. Stirring was continued at that temperature until completion of the reaction. The volatiles were removed in vacuo, the residual oil was dissolved in diethyl ether, and a solution of ethanolamine (2.4 equiv.) in THF (1.4 M) was added causing spontaneous precipitation of the 9-BBN·ethanolamine adduct. The suspension was stirred for 2.5h, the white precipitate was filtered off and the filtrate was evaporated under reduced pressure to give an oil. Purification by flash column chromatography on silica gel using 40% diethyl ether – petroleum ether as eluent afforded the title compound in 82% yield.

^1H NMR (500 MHz, $CDCl_3$) δ: 6.44 (d, J = 1.9Hz, 2H), 6.17 (t, J = 1.9Hz, 1H), 5.66 (d, J = 11.0Hz, 1H), 5.28(dt, J = 11.0Hz, J = 7.3Hz, 1H), 5.14(brs, 2H, OH), 2.01 – 1.85(m, 4H), 1.80 – 1.65(m, 6H), 1.15 – 1.07(m, 4H), 0.77(t, J

= 6.8Hz, 3H).

Resorcinol compound 1c (shown in Scheme 3) was synthesized by the method disclosed in Papahatjis et al. *J. Med. Chem.*, 41: 1195-1200 (1998), the content of which is hereby incorporated by reference. Resorcinol compound 1d (shown in Scheme 3) was synthesized by the method disclosed in Yan Guo et al. *J. Med. Chem.*, 37: 3867-3870 (1994), the content of which is hereby incorporated by reference.

Resorcinol compound 1e (shown in Scheme 2) was synthesized by the method depicted in Scheme 2.



1e

Reagents and conditions. a) n-BuLi, -30^{0}C, THF, Br$(CH_2)_4C{\equiv}C$TMS; b) $(CF_3COO)_2IPh$, aq.MeOH; c) CH_3MgBr, Et_2O; d) $HCl_{(g)}$, CCl_4; e) Me_3Al, -30^{0}C to r.t, toluene; f) K_2CO_3, MeOH; g) BBr_3, -40^{0}C to 0^{0}C, CH_2Cl_2

Scheme 2

general procedure:

[7-(3,5-Dimethoxyphenyl-1,3-dithian-7-yl)-1-heptynyl]trimethylsilane.

A solution of 2-(3,5-dimethoxyphenyl)-1,3-dithiane (1 equiv.) in dry tetrahydrofuran (0.5 M) was cooled to -30°C under argon and n-butyllithium (1.2 equiv., 1.6 M solution in hexanes) was added dropwise. The yellow-brown reaction mixture was stirred at the same temperature for 2 hours and (6-bromo-1-hexynyl)trimethylsilane (1.2 equiv.) was added in a dropwise manner when the color changed from yellow-brown to light yellow. The reaction mixture was allowed to warm to room temperature overnight and poured into water and extracted with diethyl ether. The combined organic extracts were dried and ether removed to give the crude product which was purified on silica gel (15% diethyl ether-petroleum ether) to afford the title compound in 86% yield as an oil.

Anal. calcd. for $C_{21}H_{32}O_2S_2Si$ C, 61.72; H, 7.89; found C, 61.49; H, 8.24.

[7-(3,5-Dimethoxyphenyl)-7-oxo-1-heptynyl]trimethylsilane.

A solution of [7-(3,5-dimethoxyphenyl-1,3-dithian-7-yl)-1-heptynyl] trimethylsilane (1 equiv.) in 10% aqueous methanol (0.1 M) was cooled in an ice-bath and bis(trifluoroacetoxy)iodobenzene (1.5 equiv.) was added portionwise with stirring. The reaction mixture was stirred for an additional 10 min and poured into sodium bicarbonate solution. The mixture was extracted with diethyl ether, ether extracts were combined, dried and solvent removed to afford an oil which was chromatographed on silica gel to afford the title compound in 90% yield.

Anal. calcd. for $C_{18}H_{26}O_3Si$ C, 67.88; H, 8.23; found C, 67.56; H, 8.55

[7-(3,5-Dimethoxyphenyl)-7-methyl-1-octynyl]trimethylsilane.

[7-(3,5-Dimethoxyphenyl)-7-oxo-1-heptynyl]trimethylsilane (1 equiv.) was dissolved in anhydrous ether (0.5 M), the solution was cooled in an ice-bath under argon and methylmagnesium bromide (2 equiv., 3M solution in diethyl

ether) was added dropwise. The light gray solution was allowed to warm to room temperature and stirred for an additional hour. The reaction mixture was poured into saturated ammonium chloride solution, the organic phase was separated and the aqueous phase was extracted with diethyl ether. The combined organic extracts were dried and ether removed to afford pure [7-(3,5-dimethoxyphenyl)-7-hydroxy-1-octynyl]trimethylsilane as a viscous oil after passing through a short silica gel column, in 95% yield.

The above tertiary carbinol (1 equiv.) was dissolved in anhydrous carbon tetrachloride (0.5 M) and dry hydrogen chloride gas was bubbled through for 1 hour. The solution was transferred to a separatory funnel with the aid of more carbon tetrachloride, washed with water and 10% sodium bicarbonate solution. The organic phase was dried and rotary evaporated to afford an oil which was passed through a short silica gel column to give pure [7-chloro-7-(3,5-dimethoxyphenyl)-1-octynyl]trimethylsilane.

A solution of the above chloride (1 equiv.) in dry toluene was cooled to -30°C under argon and trimethylaluminum (2 equiv., 2M solution in toluene) was added in a slow dropwise manner. The resulting clear reaction mixture was stirred at room temperature for about 16 hours and then 5% aqueous hydrochloric acid was added in a very cautious manner. The organic layer was separated, washed with water, dried and toluene removed. The residual oil was chromatographed on silica gel to afford the title compound as colorless oil.

^{1}H NMR ($CDCl_3$) δ 6.47 (d, J=2.16 Hz, 2H), 6.28 (t, J=2.16 Hz, 1H), 3.78 (s, 6H), 2.14 (t, J=7.08 Hz, 2H), 1.63-1.06 [overlapping patterns i.e., 1.63-1.06 (m, 6H), 1.25 (s, 6H)], 0.10 (s, 9H).

Anal. calcd. for $C_{20}H_{32}O_2Si$ C, 72.23; H, 9.70; found C, 71.98; H, 9.87.

7-(3,5-Dimethoxyphenyl)-7-methyl-1-octyne.

[7-(3,5-Dimethoxyphenyl)-7-methyl-1-octynyl]trimethylsilane (1 equiv.) was dissolved in anhydrous methanol (0.8 M), anhydrous potassium carbonate

(0.2 equiv.) was added and the heterogeneous mixture was stirred at room temperature, under argon, for 24 hours. The reaction mixture was diluted with water and extracted with diethyl ether. The ether extract was dried, concentrated by rotary evaporation and the residue was purified by chromatography on silica gel (5% diethyl ether-petroleum ether) to give the title compound in 76% yield.

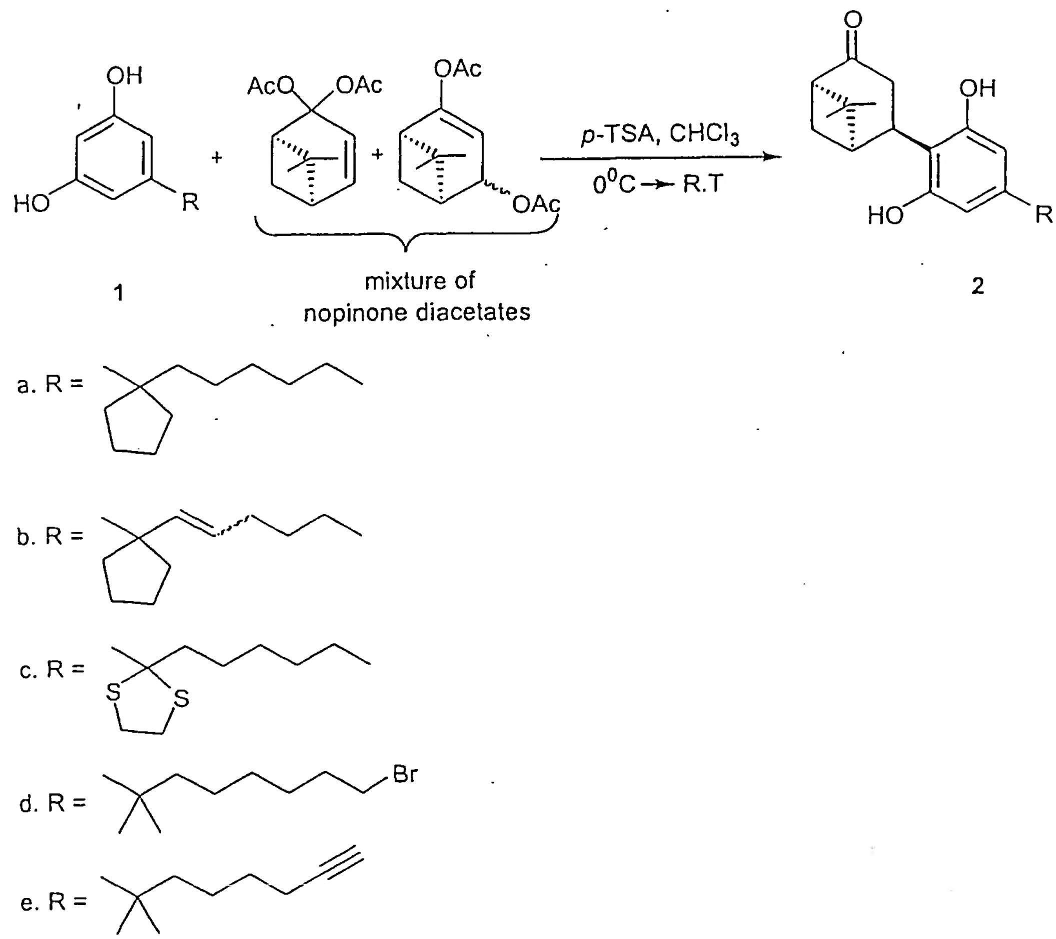
3-(1,1-Dimethylhept-6-ynyl)resorcinol, (compound 1e)

A solution of 7-(3,5-dimethoxyphenyl)-7-methyl-1-octyne (1 equiv.) in anhydrous dichloromethane (0.1 M) was cooled to -40°C under argon and boron tribromide (2.5 equiv., 1M solution in dichloromethane) was added via syringe. The reaction mixture was allowed to warm to 0°C with stirring over a period of 1-1.5 hours and then quenched with saturated sodium bicarbonate. The organic layer was separated, dried and solvent removed. The residue was chromatographed on silica gel (30-40% diethyl ether-petroleum ether) to give the title resorcinol in 56% yield.

^{13}C NMR ($CDCl_3$) δ 156.37, 153.11, 105.92, 100.11, 84.76, 68.22, 55.30, 43.77, 37.70, 29.03, 28.79, 23.87, 18.24.

2. Bicyclic cannabinoid synthesis

The bicyclic ketones (compound 2 with, for example, R groups a, b, c, d or e shown in Scheme 3) were synthesized by the method depicted in Scheme 3.



Scheme 3

general procedure:

To a solution of resorcinol (1 equiv.) and nopinone diacetates (approximately 1.3 equiv., ca. 87% pure by ^1H NMR) in chloroform (approximately 0.1M) at 0°C was added *p*-toluene sulfonic acid monohydrate (approximately 1.3 equiv.). Following the addition, the reaction temperature was raised to room temperature and stirring was continued for 4 hours to 3 days to ensure complete formation of the product. The reaction mixture was diluted

with an organic solvent and washed sequentially with water, saturated aqueous sodium bicarbonate, and brine. The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel to afford the bicyclic ketone.

compound 2a

(4*R*)-4-[4-(1′,1′-cyclopentylheptyl)-2,6-dihydroxyphenyl]-6,6-dimethyl-2-norpinanone. Yield: 49%; white solid; mp = 187-188°C.

compound 2b

(4*R*)-4-[4-(1′,1′-cyclopentylhept-2′-enyl)-2,6-dihydroxyphenyl]-6,6-dimethyl-2-norpinanone. Yield: 47%; white solid; mp = 167-168°C.

compound 2c

(4*R*)-4-[4-(2-hexyl-1,3-dithiolan-2-yl)-2,6-dihydroxyphenyl]-6,6-dimethyl-2-norpinanone. Yield: 13%; white solid; mp = 160-161°C dec.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.68(s, 2H, ArH), 5.02(brs, 2H, OH), 3.95(t, J = 8.2Hz, 1H), 3.44 (dd, J = 18.7Hz, J = 7.8Hz, 1H), 3.37 – 3.30 (m, 2H), 3.25 –3.18 (m, 2H), 2.60 (dd, J = 19.5Hz, J = 8.5Hz, 1H), 2.58 (t, J = 4.7Hz, 1H), 2.53 – 2.49 (m, 1H), 2.44 (d, J = 10.8Hz, 1H), 2.30 (m, 1H), 2.26 – 2.22 (m, 2H), 1.36 (s, 3H), 1.27 –1.19 (m, 8H), 0.99 (s, 3H), 0.85 (t, J = 6.5Hz, 3H).

compound 2d

(4*R*)-4-[4-(7′-bromo-1′,1′-dimethylheptyl)-2,6-dihydroxyphenyl]-6,6-dimethyl-2-norpinanone. Yield: 41%; light yellow solid. The title compound (2d) was used in the preparation of the derivative compound 4d.

Anal. calcd. for $C_{24}H_{34}BrO_2$ C, 63.85; H, 7.81; found C, 63.99; H, 8.20.

compound 2e

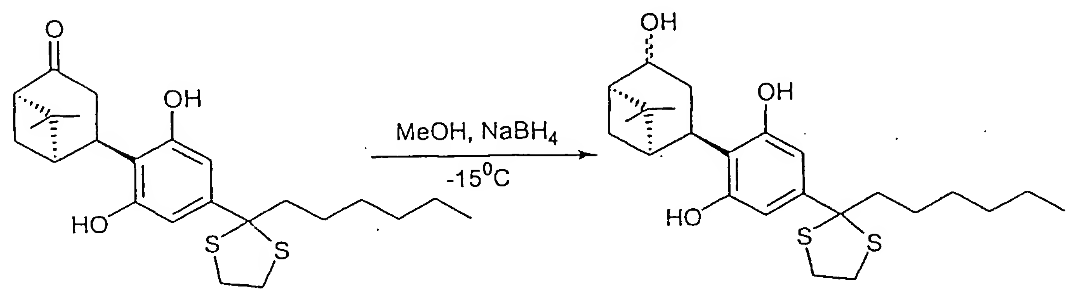
(4*R*)-4-[4-(1',1'-dimethylhept-6'-ynyl)-2,6-dihydroxyphenyl]-6,6-dimethyl-2-norpinanone. Yield: 40%. The title compound (2e) was used in the preparation of the derivative compound 4e.

FAB HRMS calcd for $C_{24}H_{32}O_3$ 369.2430 (M+H$^+$); found 369.2430.

compound 3

Synthesis of a diastereomeric mixture of (4*R*)-4-[4-(2-hexyl-1,3-dithiolan-2-yl)-2,6-dihydroxyphenyl]-6,6-dimethyl-2β-norpinanol and (4*R*)-4-[4-(2-hexyl-1,3-dithiolan-2-yl)-2,6-dihydroxyphenyl]-6,6-dimethyl-2α-norpinanol.

The title mixture (compound 3) was synthesized by the method depicted in Scheme 4 below.



2c 3

Scheme 4

procedure:

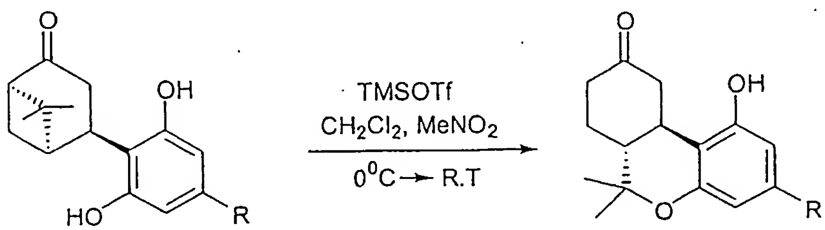
To a stirred solution of (4R)-4-[4-(2-hexyl-1,3-dithiolan-2-yl)-2,6-dihydroxyphenyl]-6,6-dimethyl-2-norpinanone (compound 2c) (11 mg, 0.025 mmol) in methanol (0.5ml) at −15°C under an argon atmosphere was added sodium borohydride (3 mg 0.079 mmol). The reaction was stirred at the same temperature for 2.5 hours and upon completion was quenched by the addition of saturated aqueous ammonium chloride. The volatiles were removed in vacuo and the residue was extracted with ethyl acetate. The organic layer was washed

with water and brine, dried over $MgSO_4$ and the solvent evaporated. The residue was chromatographed on silica gel to afford 6 mg (54%) of the title mixture as a white glassy.

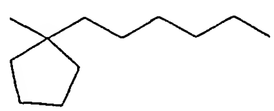
Preparation of compounds of compound formula IV, V, VI.

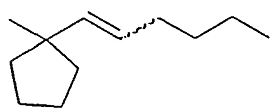
3. 9-Nor-9-oxohexahydrocannabinol synthesis

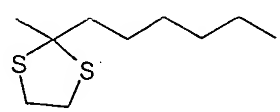
The 9-Nor-9-oxohexahydrocannabinols (compound 4 with, for example, R groups a, b, c, d and e shown in Scheme 5) were synthesized by the method depicted in Scheme 5.

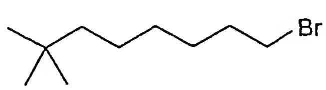


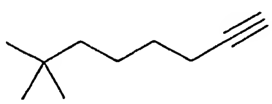
2 4

a. R = 

b. R = 

c. R = 

d. R = 

e. R = 

Scheme 5

general procedure:

To a stirred solution of bicyclic ketone (1 equiv.) in a mixture of dry methylene chloride-nitromethane (approximately 0.01-0.05M) at 0°C, under an argon atmosphere was added trimethylsilyl trifluoromethanesulfonate (approximately 0.3-1.3 equiv.). Following the addition, the mixture was stirred from 0°C to room temperature for 1-7 hours. The reaction was quenched with saturated aqueous sodium bicarbonate / brine (1:1), and organic solvent was added. The organic phase was separated, the aqueous phase was extracted with organic solvent, and the combined organic phase was washed with brine and dried over $MgSO_4$. Solvent evaporation followed by flash column chromatography on silica gel afforded 9-Nor-9-oxohexahydrocannabinols.

compound 4a

(-)-trans-3-(1',1'-cyclopentylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b,d*]pyran-9-one. Yield: 75%; White foam.

compound 4b

(-)-trans-3-(1',1'-cyclopentylhept-2'-enyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b,d*]pyran-9-one. Yield: 73%; White foam.

compound 4c

(-)-trans-3-(2-hexyl-1,3-dithiolan-2-yl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b,d*]pyran-9-one. Yield: 83%; White foam; mp = 62-64°C dec.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.76 (d, J = 1.8Hz, 1H, ArH), 6.64 (d, J = 1.8Hz, 1H, ArH), 5.85 (s, 1H, OH), 3.94 (d, J = 14.6Hz, 1H), 3.36-3.30 (m, 2H), 3.28-3.21 (m, 2H), 2.87 (td, J = 11.9Hz, J = 3.3Hz, 1H), 2.63-2.59 (m, 1H), 2.48-2.40 (m, 1H), 2.27 (m, 2H), 2.18-2.14 (m, 2H), 1.96 (td, J =

11.7Hz, J = 2.0Hz, 1H), 1.56-1.45 (m, 4H), 1.26-1.19 (m, 8H), 1.12 (s, 3H), 0.84 (t, J = 7.0Hz, 3H).

compound 4d

(-)-trans-3-(7'-bromo-1',1'-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9*H*-dibenzo[*b,d*]pyran-9-one. Yield: 71%; light yellow foam. The title compound (4d) was used in the preparation of the derivative compound 6d.

Anal. calcd. for $C_{24}H_{34}BrO_2$ C, 63.85; H, 7.81; found C, 63.99; H, 8.20.

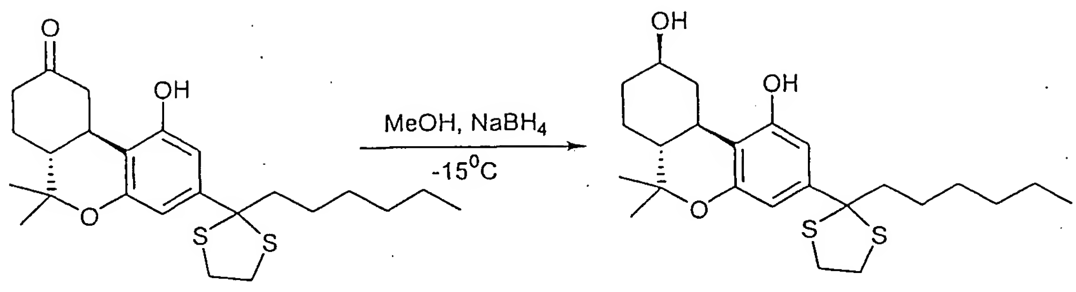
compound 4e

(-)-trans-3-(1',1'-dimethylhept-6'-ynyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo[b,d]pyran-9-one. Following the general workup, the residue passed through a short column of silica gel and the title compound (4e) was used in the preparation of the derivative compound 6e without further purification.

4. 9-Nor-9β-hydroxyhexahydrocannabinol synthesis

compound 5

6a,7,8,9,10,10a-Hexahydro-3-(2-hexyl-1,3-dithiolan-2-yl)-6,6-dimethyl-6*H*-dibenzo[*b,d*]pyran-1,9β-diol, was synthesized by the method depicted in Scheme 6.



4c 5

Scheme 6

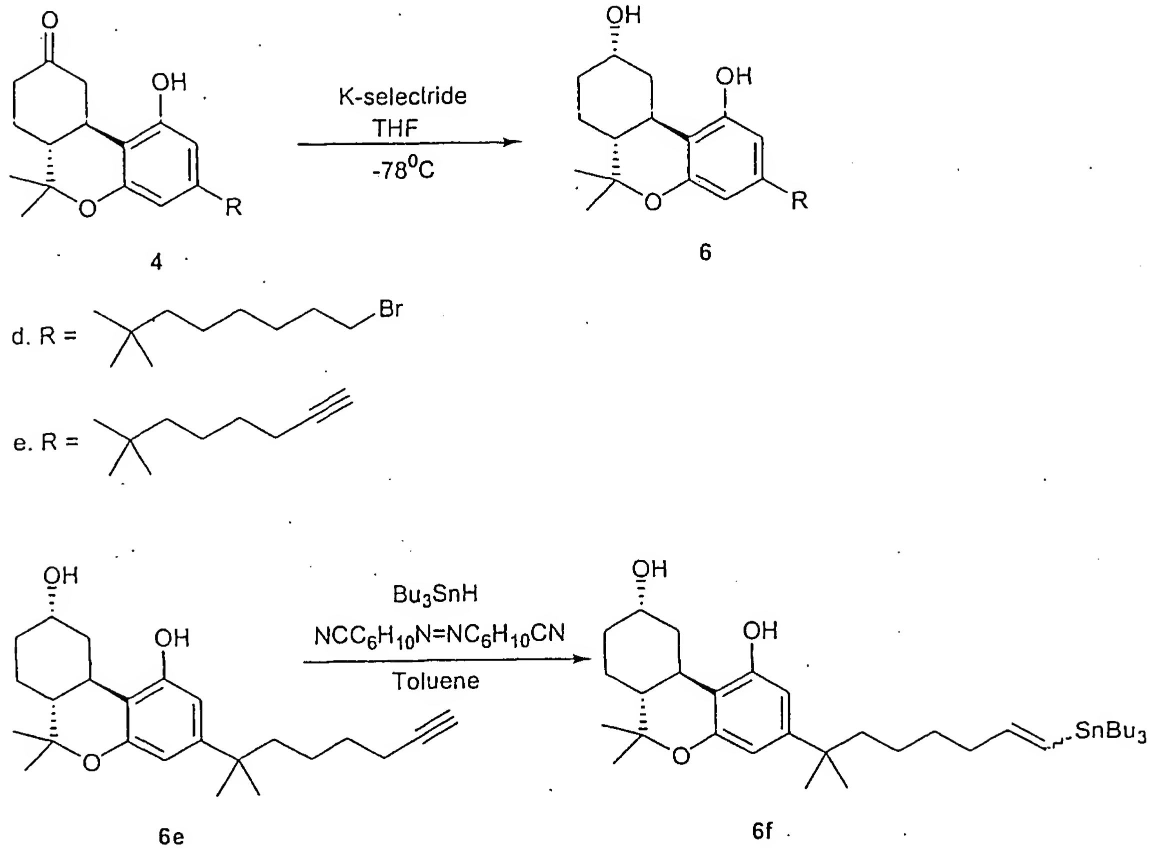
procedure:

To a stirred solution of (-)-trans-3-(2-hexyl-1,3-dithiolan-2-yl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo[b,d]pyran-9-one (compound 4c) (1 equiv.) in methanol (approximately 0.05M) at -15^0C under an argon atmosphere was added sodium borohydride (approximately 5 equiv.). The reaction was stirred at the same temperature and upon completion was quenched by the addition of saturated aqueous ammonium chloride. The volatiles were removed in vacuo and the residue was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$ and the solvent evaporated. The residue was chromatographed on silica gel to afford the title compound in 69% yield.

^{1}H NMR ($CDCl_3$) δ: 6.70 (d, J = 1.7Hz, 1H, ArH), 6.59 (d, J = 1.7Hz, 1H, ArH), 5.98 (brs, 1H), 3.89-3.84 (m, 1H, H-9), 3.51-3.49 (m, 1H), 3.34-3.21 (m, 4H), 2.47 (t, J = 10.8Hz, 1H), 2.30-1.37 (11H, especially 1.38, s Me), 1.26-1.16 (m, 8H), 1.06 (s, 3H, Me), 0.84 (t, J = 6.9Hz, 3H).

5. 9-Nor-9α-hydroxyhexahydrocannabinol synthesis

The 9-Nor-9α-hydroxyhexahydrocannabinols (compound 6 with, for example, R groups d and e shown in Scheme 7) were synthesized by a method depicted in Scheme 7 below.



Scheme 7

general procedure:

A solution of 9-nor-9-oxohexahydrocannabinol (1 equiv.) in anhydrous THF (approximately 0.02M) was cooled to −78 °C under argon and a 1 M solution of K-selectride in THF (approximately 5 equiv.) was added in a slow, dropwise manner. The reaction mixture was stirred at −78 °C for 2-5 hours and then quenched by cautious addition of water. The mixture was warmed to room temperature poured into 10% hydrochloric acid and the organic layer was separated. The aqueous layer was extracted the combined organic layer dried ($MgSO_4$) and solvent evaporated. The residue was chromatographed on silica gel to afford 9-Nor-9α-hydroxyhexahydrocannabinols.

compound 6d

6a,7,8,9,10,10a-Hexahydro-3-(7'-bromo-1',1'-dimethylheptyl)-6,6-dimethyl-6*H*-dibenzo[*b,d*]pyran-1,9α-diol. Yield: 60%. The title compound (6d) was used in the preparation of the derivative compound 7d.

compound 6e

6a,7,8,9,10,10a-Hexahydro-3-(1',1'-dimethylhept-6'-ynyl)-6,6-dimethyl-6*H*-dibenzo[*b,d*]pyran-1,9α-diol. The title compound (6e) was used in the preparation of the derivative compound 6f.

FAB HRMS calcd for $C_{24}H_{34}O_3$ 371.2589 (M+H$^+$); found 371.2588.

compound 6f

6a,7,8,9,10,10a-Hexahydro-3-(7'-tri-n-butyltin-1',1'-dimethylhept-6'-enyl)-6,6-dimethyl-6*H*-dibenzo[*b,d*]pyran-1,9α-diol.

procedure:

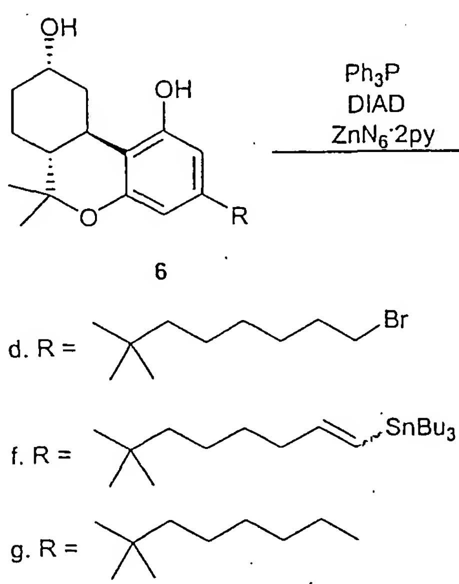
A mixture of 3-(1',1'-dimethylhept-6'-ynyl)-9α-hydroxyhexahydrocannabinol (compound 6e)

(100 mg, 0.27 mmol), 1,1'-azobis(cyclohexanecarbonitrile) (20 mg) and 0.16 mL of tri-n-butyltin hydride in 5.3 mL of dry toluene was refluxed for 10 h under argon. The mixture was cooled to room temperature, toluene was removed *in vacuo* and the residue was chromatographed on silica gel (30-50% ethyl ether-petroleum ether) to afford 130 mg (73%) of the title compound (6f) as a colorless oil.

FAB HRMS calcd for $C_{36}H_{63}O_3Sn$ 663.3799 (M+H$^+$); found 663.3798.

6. 9-Nor-9β-azidohexahydrocannabinol synthesis

The 9-Nor-9β-azidohexahydrocannabinols (compound 7 with, for example, R groups d, f and g shown in Scheme 8) were synthesized by the method depicted in Scheme 8.



Scheme 8

general procedure:

A mixture of 9-Nor-9α-hydroxyhexahydrocannabinol (1 equiv.), zinc azide bipyridyl complex (approximately 1.5 equiv), triphenylphosphine (approximately, 4 equiv.) anhydrous organic solvent (approximately 0.25M) was stirred under argon and a solution of diisopropyl azodicarboxylate (DIAD, approximately 4 equiv.) in dry organic solvent was added in slow dropwise manner. The mixture was allowed to stir at room temperature and upon completion chromatographed on a silica gel column to afford the 9-Nor-9β-azidohexahydrocannabinols.

compound 7d

1-Hydroxy-3-(7'-bromo-1',1'-dimethylheptyl)-6,6-dimethyl-9β-azido-6a,7,8,8,10,10a-hexahydro-6*H*-dibenzo[*b,d*]pyran. Yield 71%; The title compound (7d) was used in the preparation of the compound 8.

compound 7f

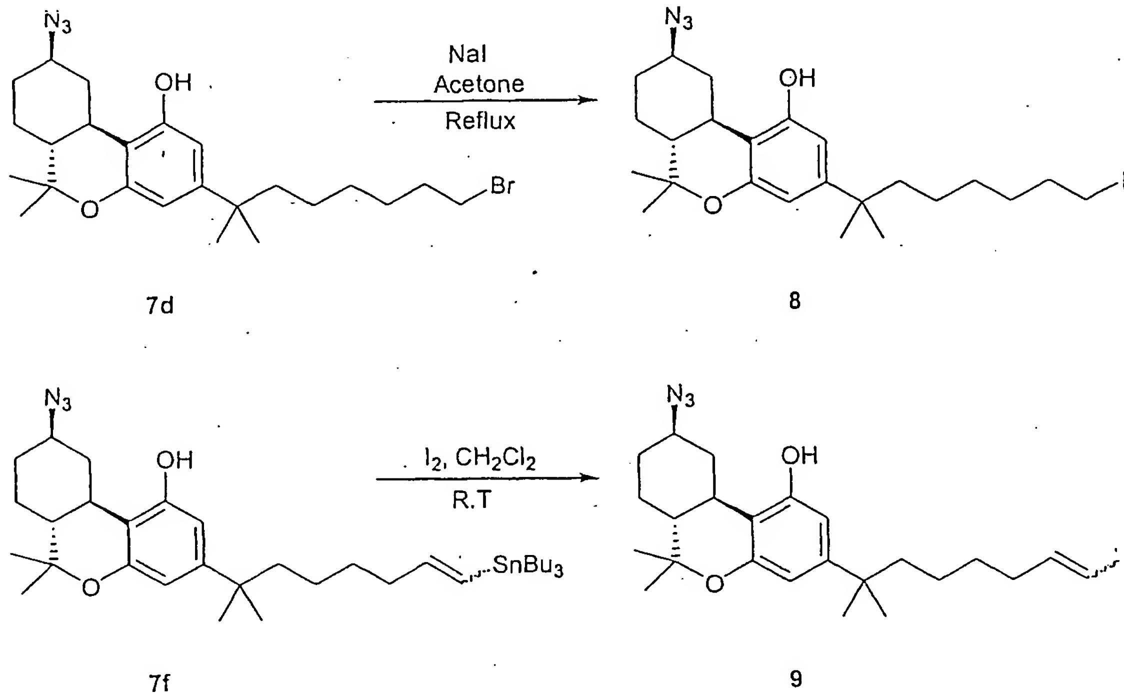
1-Hydroxy-3-(7'-tri-n-butyltin-1',1'-dimethylhept-6'-enyl)-6,6-dimethyl-9β-azido-6a,7,8,8,10,10a-hexahydro-6*H*-dibenzo[*b,d*]pyran. Yield 72%; The title compound (7f) was used in the preparation of the compound 9.

compound 7g

1-Hydroxy-3-(1',1'-dimethylheptyl)-6,6-dimethyl-9β-azido-6a,7,8,8,10,10a-hexahydro-6*H*-dibenzo[*b,d*]pyran. Yield 75%. The precursor for the title compound was synthesized by the method previously described for compound 6.

IR (AgCl) : ν = 2096 cm^{-1} (N_3).

The 9-Nor-9β-azidohexahydrocannabinols (compounds 8 and 9 shown in Scheme 9) were synthesized by the method depicted in Scheme 9.



Scheme 9

compound 8

1-Hydroxy-3-(7'-iodo-1',1'-dimethylheptyl)-6,6-dimethyl-9β-azido-6a,7,8,8,10,10a-hexahydro-6H-dibenzo[b,d]pyran. The title compound (8) was synthesized by the method depicted in Scheme 9.

procedure:

100 mg (0.21 mmol) of 9β-azido-3-(7′-bromo-1′,1′-dimethylheptyl) hexahydrocannabinol (compound 7d) was dissolved in 5 ml of dry acetone, 63 mg (0.42 mmol) of sodium iodide was added and the solution was refluxed for 6 hours. Acetone was removed by rotary evaporation and the residue was extracted in ether. The ether extract was concentrated and the residue chromatographed to afford 88 mg (80%) of the title compound (8) as a gum.

compound 9

1-Hydroxy-3-(7'-iodo-1',1'-dimethylhept-6'-enyl)-6,6-dimethyl-9β-azido-6a,7,8,8,10,10a-hexahydro-6H-dibenzo[b,d]pyran. The title compound (9) was synthesized by a method depicted in Scheme 9.

procedure:

16 mg (0.023 mmol) of 9-Nor-9β-azidohexahydrocannabinol (compound 7f) was dissolved in 1 mL of dichloromethane and a solution of 8.7 mg (0.034 mmol) of iodine in 0.5 mL of dichloromethane was added dropwise. The solution was stirred at room temperature for 15 min and excess iodine was destroyed by adding a 0.1 M aqueous solution of sodium hydrogen sulfite. The organic layer was separated, dried ($MgSO_4$) and solvent removed. The residue was purified by column chromatography on silica gel to afford 12.8 mg of the title compound (9).

FAB HRMS calc'd for $C_{24}H_{34}IN_3O_2$ 524.1744 ($M+H^+$); found 524.1771.

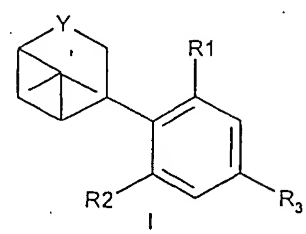
Generally, the synthesis of compounds 2a-2e, 3, 4a-4e, 5, 6d-6f, 7d-7g, 8 and 9 was accomplished by the stereospecific condensation (Scheme 3, Scheme 5) of nopinone diacetates with an appropriately substituted resorcinol. On the other hand the requisite mixture of nopinone diacetates was prepared by the method disclosed in Drake et al. *J.Med. Chem.*, 3596 (1998). This method involves isopropenyl acetate based transesterification followed by lead tetraacetate oxidation with no loss of optical purity starting from commercially available (1R, 5S)-(+)-nopinone. Since (1S, 5R)-(-)-nopinone of respectable optical purity can be obtained from commercially available (+)-β-pinene or (+)-α-pinene by the method disclosed in Brown et al. *J. Org. Chem.*, 1217 (1990) and in Lavalle'e et al. *J. Org. Chem.*, 1362 (1986) respectively, the enantiomers of the above mentioned compounds could be synthesized following the same methodology. Each of the above references is incorporated by reference herein.

The inventive analogs described herein, and physiologically acceptable salts thereof, have high potential when administered in therapeutically effective amounts for providing a physiological effect useful to treat pain; peripheral pain; glaucoma; epilepsy; nausea such as associated with cancer chemotherapy; AIDS Wasting Syndrome; cancer; neurodegenerative diseases including Multiple Sclerosis, Parkinson's Disease, Huntington's Chorea and Alzheimer's Disease; to enhance appetite; to reduce fertility; to prevent or reduce diseases associated with motor function such as Tourette's syndrome; to provide neuroprotection; to produce peripheral vasodilation and to suppress memory. Thus, another aspect of the invention is the administration of a therapeutically effective amount of an inventive compound, or a physiologically acceptable salt thereof, to an individual or animal to provide a physiological effect.

Those skilled in the art will recognize, or be able to ascertain with no more than routine experimentation, many equivalents to the specific embodiments of the invention disclosed herein. Such equivalents are intended to be encompassed by the scope of the invention.

What Is Claimed Is:

1. A compound of formula I below, and physiologically acceptable salts, comprising:



I

wherein Y comprises =C=O, $=CH-(CH_2)_f-Y_1-(CH_2)_g-Y_2$, $=C=N-Y_3$, $=CH-NY_4Y_5$, $=CH-(CH_2)_h-Y_6$, $-C(O)N(Y_7)-$, $-N(Y_7)C(O)-$, $=NY_{11}$, $=N-(CH_2)_f-Y_1-(CH_2)_g-Y_2$, a spirocycle, or CY_9Y_{10}, including all isomers;

Y_1 independently comprises O, CO, C(O)O, OCO or CH_2;

Y_2 independently comprises H, halogen, CN, CF_3, N_3, OH, COOH, alkoxy,
acyloxy, NCS, NCO or NY_7Y_8;

Y_3 independently comprises –OH, $-NH_2$, alkoxy, alkyl, $-(CH_2)_n-NR_{10}R_{11}$, $-(CH_2)_n-CO_2R$ where R comprises H or alkyl, $-O-(CH_2)_n-NR_{10}R_{11}$, $-O-(CH_2)_n-CO_2R$ or $-O-(CH_2)_n-CONR_{10}R_{11}$;

Y_4 independently comprises H, OH, alkoxy or alkyl;

Y_5 independently comprises H, OH, alkoxy or alkyl, wherein Y_4 and Y_5 cannot both be OH and wherein Y_4 and Y_5 cannot both be alkoxy;

Y_6 independently comprises H, halogen, CN, COOH, COalkyl, CF_3, SO_2alkyl, COfluoroalkyl, N_3, OH, alkoxy, acyloxy, NCS, NCO or NY_7Y_8;

Y_7 independently comprises H, alkyl, hydroxyalkyl, an aromatic ring, an aromatic ring substituted by at least one member selected from alkyl, alkoxy, halogen and CF_3, a heterocyclic ring or a heteroaromatic ring;

Y_8 independently comprises H, alkyl, hydroxyalkyl, an aromatic ring, an aromatic ring substituted by at least one member selected from alkyl, alkoxy,

halogen and CF_3, a heterocyclic ring or a heteroaromatic ring; or alternatively, Y_7 and Y_8 taken together comprise part of a 3 to 7 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S;

Y_9 independently comprises H, alkyl or alkoxycarbonylmethyl;

Y_{10} independently comprises H, alkyl or alkoxycarbonylmethyl;

Y_{11} independently comprises H, alkyl, CO, CN, CO–alkyl, SO_2–akyl or CF_3; f comprises an integer from 0 to about 5;

g comprises an integer from 0 to about 5;

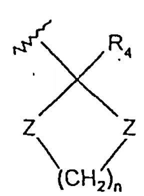
h comprises an integer from 0 to about 5;

n comprises an integer from 0 to about 4;

R_1 and R_2 each independently comprise H, OH, halogen, alkyl, –O–alkyl, NH_2, NO_2, CN, acyl, aroyl, benzoyl, substituted benzoyl, arylalkyl, substituted arylalkyl, phenacyl, substituted phenacyl, –O–alkyl–$NR_{10}R_{11}$, –O–alkyl–COOR where R comprises H or alkyl, –O–alkyl–$CONR_{10}R_{11}$, $OCOCH_3$, –N(alkyl)$_2$, –CO(alkyl)X or –OCO(alkyl)X where X comprises H, dialkylamino, a cyclic amine, a carbocyclic ring, a heterocyclic ring, an aromatic ring or a heteroaromatic; and

R_{10} and R_{11} each independently comprise H, alkyl, hydroxyalkyl or R_{10} and R_{11} together comprise part of a 3 to 7 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S.

2. The compound of claim 1 wherein R_3 comprises:



wherein each Z independently comprises $CR_{12}R_{13}$ where R_{12} and R_{13} each independently comprise H, alkyl, S, O, NH, $N(CH_3)$, SO or SO_2;

R_4 comprises $-(CH_2)_j-R_5$, $-(CH_2)_j-A-(CH_2)_k-R_5$ or $-(CH_2)_j-A-(CH_2)_k-B-R_5$;

A and B each independently comprise $-CH_2-CH_2-$, $-CH=CH-$, $-C\equiv C-$, O, S, SO, SO_2 or NH;

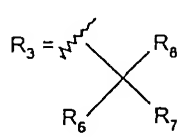
R_5 comprises H, halogen, CN, CF_3, N_3, COOH, NH_2, $N(CH_3)_2$, $\oplus N(CH_3)_3$, Sn(alkyl)$_3$, phenyl, COOR where R comprises H or alkyl, a carbocylic ring, a heterocyclic ring, an aromatic ring, a heteroaromatic ring, a polycarbocyclic ring structure having 2 to about 5 rings, a polyheterocyclic ring structure having 2 to about 5 rings or $CONR_{10}R_{11}$ where R_{10} and R_{11} each independently comprise H, alkyl, hydroxyalkyl or R_{10} and R_{11} together comprise part of a 5 or 6 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S;

n comprises an integer from 0 to about 4;

j comprises an integer from 0 to about 7; and

k comprises an integer from 0 to about 7.

3. The compound of claim 1 wherein R_3 comprises:



wherein R_6 and R_7 each independently comprise H or alkyl;

R_8 comprises $-(CH_2)_j-C\equiv C-(CH_2)_k-R_9$;

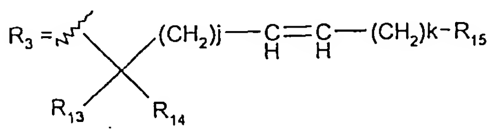
R_9 comprises H, halogen, CN, CF_3, N_3, COOH, NH_2, $N(CH_3)_2$, $\oplus N(CH_3)_3$, Sn(alkyl)$_3$, phenyl, COOR where R comprises H or alkyl, a carbocylic ring, a heterocyclic ring, an aromatic ring, a heteroaromatic ring, a polycarbocyclic ring structure having 2 to about 5 rings, a polyheterocyclic ring structure having 2 to about 5 rings or $CONR_{10}R_{11}$ where R_{10} and R_{11} each independently comprise H, alkyl, hydroxyalkyl or R_{10} and R_{11} together comprise part of a 5 or 6 membered saturated heterocyclic ring containing up to one additional heteroatom selected

from N, O and S;

j comprises an integer from 0 to about 7; and

k comprises an integer from 0 to about 7.

4. The compound of claim 1, wherein R_1 and R_2 each independently comprise H, OH, alkyl or alkoxy and R_3 comprises:



wherein R_{13} and R_{14} each independently comprise H or alkyl;

R_{15} comprises H, halogen, CN, CF_3, N_3, COOH, NH_2, $N(CH_3)_2$, $\oplus N(CH_3)_3$, $Sn(alkyl)_3$, phenyl, COOR where R comprises H or alkyl, a carbocylic ring, a heterocyclic ring, an aromatic ring, a heteroaromatic ring, a polycarbocyclic ring structure having 2 to about 5 rings, a polyheterocyclic ring structure having 2 to about 5 rings, or $CONR_{10}R_{11}$ where R_{10} and R_{11} each independently comprise H, alkyl, hydroxyalkyl or R_{10} and R_{11} together comprise part of a 5 or 6 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S;

j comprises an integer from 0 to about 7; and

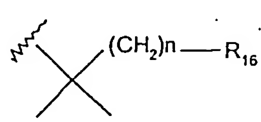
k comprises an integer from 0 to about 7.

5. The compound of claim 1 wherein Y comprises $=CH-(CH_2)_h-Y_6$;

Y_6 comprises I, CN or N_3 and h comprises an integer from about 1 to about 3, or Y_6 comprises I or N_3 and h comprises an integer from 0 to about 3;

R_1 and R_2 each independently comprise H, OH, alkyl or alkoxy;

R_3 comprises:

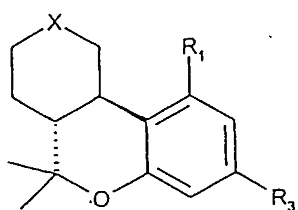


wherein R_{16} comprises H, halogen, CN, CF_3, N_3, COOH, NH_2,

$N(CH_3)_2$, $\oplus N(CH_3)_3$, Sn(alkyl)$_3$, phenyl, COOR where R comprises H or alkyl, a carbocylic ring, a heterocyclic ring, an aromatic ring, a heteroaromatic ring, a polycarbocyclic ring structure having 2 to about 5 rings, a polyheterocyclic ring structure having 2 to about 5 rings or $CONR_{10}R_{11}$ where R_{10} and R_{11} each independently comprise H, alkyl, hydroxyalkyl or R_{10} and R_{11} together comprise part of a 5 or 6 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S; and

n comprises an integer from 0 to about 7.

6. A compound of formula IV below, and physiologically acceptable salts, comprising:



IV

wherein X comprises =C=O, $=CH-(CH_2)_f-X_1-(CH_2)_g-X_2$, $=C=N-X_3$, $=CH-NX_4X_5$, $=CH-(CH_2)_h-X_6$, $-C(O)N(X_7)-$, $-N(X_7)C(O)-$, $=NX_{11}$, $=N-(CH_2)_f-X_1-(CH_2)_g-X_2$, a spirocycle, or CX_9X_{10}, including all isomers;

X_1 independently comprises O, CO, C(O)O, OCO or CH_2;

X_2 independently comprises H, halogen, CN, CF_3, N_3, OH, COOH, alkoxy, acyloxy, NCS, NCO or NX_7X_8;

X_3 independently comprises $-OH$, $-NH_2$, alkoxy, alkyl, $-(CH_2)_n-NR_{10}R_{11}$, $-(CH_2)_n-CO_2R$ where R comprises H or alkyl, $-O-(CH_2)_n-NR_{10}R_{11}$, $-O-(CH_2)_n-CO_2R$ or $-O-(CH_2)_n-CONR_{10}R_{11}$;

X_4 independently comprises H, OH, alkoxy or alkyl;

X_5 independently comprises H, OH, alkoxy or alkyl, wherein X_4 and X_5 cannot both be OH and wherein X_4 and X_5 cannot both be alkoxy;

X_6 independently comprises H, halogen, CN, COOH, COalkyl, CF_3,

SO_2alkyl, COfluoroalkyl, N_3, OH, alkoxy, acyloxy, NCS, NCO or NX_7X_8;

X_7 independently comprises H, alkyl, hydroxyalkyl, an aromatic ring, an aromatic ring substituted by at least one member selected from alkyl, alkoxy, halogen and CF_3, a heterocyclic ring or a heteroaromatic ring;

X_8 independently comprises H, alkyl, hydroxyalkyl, an aromatic ring, an aromatic ring substituted by at least one member selected from alkyl, alkoxy, halogen and CF_3, a heterocyclic ring or a heteroaromatic ring; or alternatively, X_7 and X_8 taken together comprise part of a 3 to 7 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S;

X_9 independently comprises H, alkyl or alkoxycarbonylmethyl;

X_{10} independently comprises H, alkyl or alkoxycarbonylmethyl;

X_{11} independently comprises H, alkyl, CO, CN, COalkyl, SO_2alkyl or CF_3;

f comprises an integer from 0 to about 3;

g comprises an integer from 0 to about 3;

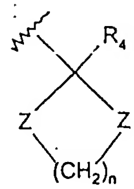
h comprises an integer from 0 to about 3;

n comprises an integer from 0 to about 4;

R_1 independently comprises H, OH, halogen, alkyl, –O–alkyl, NH_2, NO_2, CN, acyl, aroyl, benzoyl, substituted benzoyl, arylalkyl, substituted arylalkyl, phenacyl, substituted phenacyl, –O–alkyl–$NR_{10}R_{11}$, –O–alkyl–COOR where R comprises H or alkyl, –O–alkyl–$CONR_{10}R_{11}$, $OCOCH_3$, –N(alkyl)$_2$, –CO(alkyl)X or –OCO(alkyl)X where X comprises H, dialkylamino, a cyclic amine, a carbocyclic ring, a heterocyclic ring, an aromatic ring or a heteroaromatic; and

R_{10} and R_{11} each independently comprise H, alkyl, hydroxyalkyl or R_{10} and R_{11} together comprise part of a 3 to 7 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S.

7. The compound of claim 6, wherein R_3 comprises



wherein each Z independently comprises $CR_{12}R_{13}$ where R_{12} and R_{13} each independently comprise H, alkyl, S, O, NH, $N(CH_3)$, SO or SO_2;

R_4 comprises $-(CH_2)_j-R_5$, $-(CH_2)_j-A-(CH_2)_k-R_5$ or $-(CH_2)_j-A-(CH_2)_k-B-R_5$.

A and B each independently comprise $-CH_2-CH_2-$, $-CH=CH-$, $-C\equiv C-$, O, S, SO, SO_2 or NH;

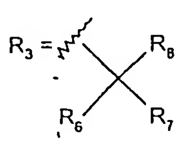
R_5 comprises H, halogen, CN, CF_3, N_3, COOH, NH_2, $N(CH_3)_2$, $\oplus N(CH_3)_3$, $Sn(alkyl)_3$, phenyl, COOR where R comprises H or alkyl, a carbocylic ring, a heterocyclic ring, an aromatic ring, a heteroaromatic ring, a polycarbocyclic ring structure having 2 to about 5 rings, a polyheterocyclic ring structure having 2 to about 5 rings or $CONR_{10}R_{11}$ where R_{10} and R_{11} each independently comprise H, alkyl, hydroxyalkyl or R_{10} and R_{11} together comprise part of a 5 or 6 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S;

n comprises an integer from 0 to about 4;

j comprises an integer from 0 to about 7; and

k comprises an integer from 0 to about 7.

8. The compound of claim 6, wherein R_3 comprises:



wherein, R_6 and R_7 each independently comprise H or alkyl;

R_8 comprises $-(CH_2)_j-C\equiv C-(CH_2)_k-R_9$;

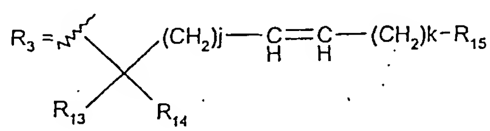
R_9 comprises H, halogen, CN, CF_3, N_3, COOH, NH_2, $N(CH_3)_2$,

$\oplus N(CH_3)_3$, $Sn(alkyl)_3$, phenyl, COOR where R comprises H or alkyl, a carbocylic ring, a heterocyclic ring, an aromatic ring, a heteroaromatic ring, a polycarbocyclic ring structure having 2 to about 5 rings, a polyheterocyclic ring structure having 2 to about 5 rings or $CONR_{10}R_{11}$ where R_{10} and R_{11} each independently comprise H, alkyl, hydroxyalkyl or R_{10} and R_{11} together comprise part of a 5 or 6 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S;

j comprises an integer from 0 to about 7; and

k comprises an integer from 0 to about 7.

9. The compound of claim 6, wherein R_1 comprises H, OH, alkyl or alkoxy and R_3 comprises:



wherein R_{13} and R_{14} each independently comprise H or alkyl;

R_{15} comprises halogen, CN, CF_3, N_3, COOH, NH_2, $N(CH_3)_2$, $\oplus N(CH_3)_3$, $Sn(alkyl)_3$, phenyl, COOR where R comprises H or alkyl, a carbocylic ring, a heterocyclic ring, an aromatic ring, a heteroaromatic ring, a polycarbocyclic ring structure having 2 to about 5 rings, a polyhéterocyclic ring structure having 2 to about 5 rings or $CONR_{10}R_{11}$ where R_{10} and R_{11} each independently comprise H, alkyl, hydroxyalkyl or R_{10} and R_{11} together comprise part of a 5 or 6 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S;

j comprises an integer from 0 to about 7; and

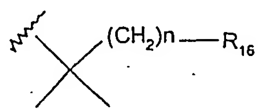
k comprises an integer from 0 to about 7.

10. The compound of claim 6 wherein X comprises $=CH-(CH_2)_h-X_6$;

X_6 independently comprises I, CN, N_3 or COOH and h comprises an integer from about 1 to about 3, or X_6 comprises I, N_3 or COOH and h comprises an integer from 0 to about 3, including all isomers;

R_1 independently comprises H, OH, alkyl or alkoxy;

R_3 comprises:



wherein R_{16} comprises H, halogen, CN, CF_3, N_3, COOH, NH_2, $N(CH_3)_2$, $\oplus N(CH_3)_3$, $Sn(alkyl)_3$, phenyl, COOR where R comprises H or alkyl, a carbocylic ring, a heterocyclic ring, an aromatic ring, a heteroaromatic ring, a polycarbocyclic ring structure having 2 to about 5 rings, a polyheterocyclic ring structure having 2 to about 5 rings or $CONR_{10}R_{11}$ where R_{10} and R_{11} each independently comprise H, alkyl, hydroxyalkyl or R_{10} and R_{11} together comprise part of a 5 or 6 membered saturated heterocyclic ring containing up to one additional heteroatom selected from N, O and S; and

n comprises an integer from 0 to about 7.

11. A pharmaceutical composition containing a therapeutically effective amount of at least one of the compounds of claims 1 through 10 and physiologically acceptable salts thereof.

12. A method of stimulating cannabinoid receptors in an individual or animal comprising administering to the individual or animal a therapeutically effective amount of at least one of the compounds of claims 1 through 10 and physiologically acceptable salts thereof.

13. A method of selectively stimulating CB2 cannabinoid receptors in an individual or animal comprising administering to the individual or animal a

therapeutically effective amount of at least one of the compounds of claims 1 through 10 and physiologically acceptable salts thereof.

14. A method of treating an individual or animal comprising administering to the individual or animal a therapeutically effective amount of at least one of the compounds of claims 1 through 10 and physiologically acceptable salts thereof.